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Carcinogen Assessment Group's Final Report on Population Risk to Ambient Benzene Exposures

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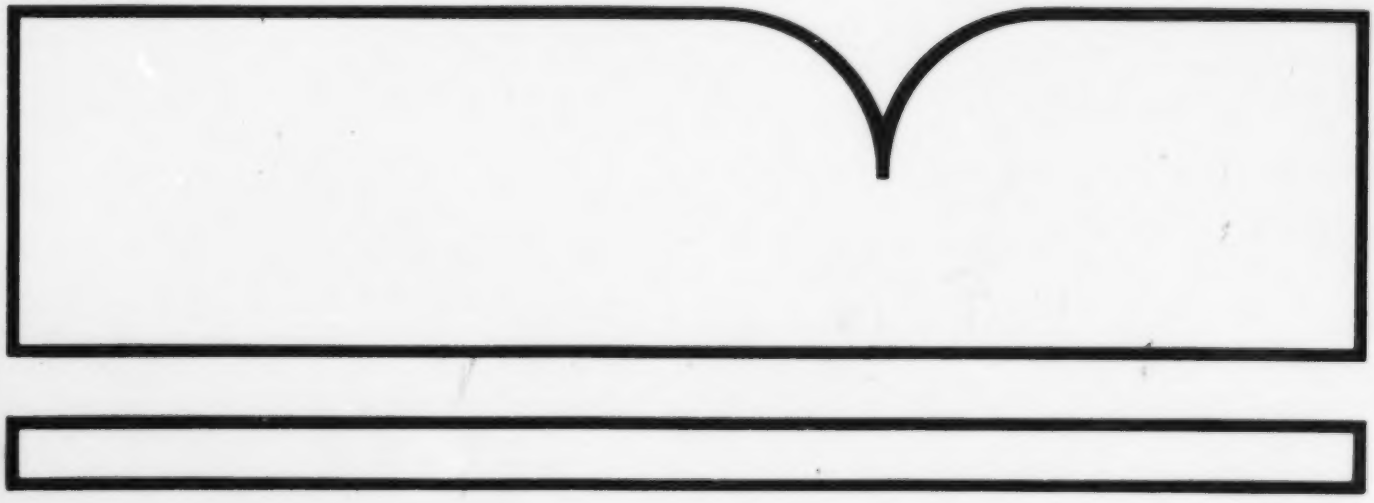

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16. ABSTRACT

This report is one of three reports which were prepared by E.P.A. to determine what regulatory action should be taken by E.P.A. to control sources of atmospheric emissions of benzene. This report estimates from three epidemiological studies the leukemia risk associated with current general population exposures to benzene in the United States. These studies were conducted by Infante, et al., (1977), Ott et al., (1977), and Askoy et al., (1977, 1976, 1974). The original report has received extensive review by the interested public and E.P.A.'s Science Advisory Board. All comments received on this first report were reviewed and considered in preparation of this report.

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Carcinogen Assessment Group's Final Report on Population Risk to Ambient Benzene Exposures

by

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Carcinogen Assessment Group

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Office of Air, Noise, and Radiation
Office of Air Quality Planning and Standards
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January 10, 1979

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CONTENTS

I Summary 1

II Introduction 3

III General Approach to Utilizing Epidemiological Studies to Predict Lifetime Probability of Cancer Deaths Due to Benzene 4

A. Mathematical Model Employed 4

B. Estimation of Lifetime Probability of Death Due to Various Forms of Leukemia for a Member of the U.S. Population 6

IV Epidemiological Studies Utilized 7

A. Infante (1977) 8

B. Askoy (1974, 1976, 1977) 13

C. Ott, et al. (1977) 17

V Estimation of Expected Number of Leukemia Deaths Due to Environmental Exposure to Benzene 21

VI Bibliography 30

VII APPENDIX - Mutagenic Risks of Benzene Exposure . . . 31

TABLES

1. Data Utilized to Estimate Lifetime Probability of Death Due to Various Forms of Leukemia 24

2. Lifetime Probability of Death in U.S. Population Due to Leukemia Type Upon Which Relative Risk in Each of the Epidemiological Studies is Based 25

3. Summary of Data Used to Estimate Lifetime Probability of a Leukemia Death Per ppm Benzene Lifetime Exposure 26

4. Source Specific Benzene Caused Leukemia Deaths/Year Based on Table I-1 of SRI Benzene Exposure Document. . 27

5. Total Exposure of People Residing in Various Locations, and Resulting Estimated Benzene Caused Leukemia Deaths/Year - Based on Table I-2 of SRI Benzene Exposure Document 27

6. Confidence Limits on Total Benzene Caused Leukemia Deaths/Year (Assumes "One-Hit" Model is the True Dose Response Relationship) 29

CARCINOGEN ASSESSMENT GROUP'S FINAL REPORT ON POPULATION RISK TO AMBIENT BENZENE EXPOSURES

I. Summary

There is substantial epidemiological evidence that benzene is a human leukemogen. However, no validated animal model has yet been developed for benzene as a carcinogen. There are several large series of case reports indicating a high risk of leukemia in individuals who developed aplastic anemia consequent to benzene exposure. In addition there are a number of epidemiological studies in the rubber, chemical and shoe industries that demonstrate an excess risk of leukemia associated with benzene exposure.

Three of these epidemiological studies provide enough information about exposure to benzene and the occurrence of leukemia to allow us to make crude quantitative estimates of the leukemia risk associated with current general population exposures to benzene in the United States. These studies were conducted by Infante et al, (1977), Ott, et al., (1977) and Askoy et al., (1977, 1976, 1974).

The Infante study, which showed an excess incidence of leukemia, is not yet completely analyzed by the authors. Hence, some assumptions made about the average duration and magnitude of exposures are necessary. The Ott study indicated a marginal excess myelogenous leukemia risk with

relatively well-documented exposures. The Askoy studies indicated a marked increase in non-lymphatic leukemia to individuals using benzene based adhesives in small shoe making shops, however, the exposure data in this situation was difficult to evaluate.

A linear non-threshold model was used to estimate the leukemia risk to the low average levels of about one part per billion to which the general population is exposed. The slope parameter of this model was taken as the geometric mean of the slope parameter estimates obtained from the three epidemiological studies. Using this extrapolation model, we estimated that the number of cases of leukemia per year in the general population due to ambient atmospheric benzene is about 90 with a 95% confidence interval from 34 to 235 assuming a precision of within two fold in the exposure estimate. This is from .23% to 1.62% of the total leukemia deaths in the United States based upon 1973 vital statistics.

The purpose of this calculation is to obtain a rough estimate of the carcinogenic hazard to benzene in the entire United States population. To do this lifetime averages of benzene exposure were estimated and these were combined with the non-threshold linear model of risk as a function of lifetime average exposure. In this report no attempt has been made to estimate the risks to selected sub-populations who may have greater or less than average exposure or sensitivity to benzene although it is certain that such groups exist.

II. Introduction

The Carcinogen Assessment Group (CAG) has been asked by the Office of Air Quality Planning and Standards (OAQPS) to estimate the carcinogenic risk to the United States population of ambient benzene concentrations. This type of information is useful in judging the overall contribution of benzene emissions to the national rates of cancer mortality, and will be used by OAQPS in the decision whether to regulate benzene.

As the basis for this estimation, the CAG is using three epidemiological studies that show a relationship between excess mortality due to leukemia and benzene exposure. Each of these studies have strengths and weaknesses that will be discussed, but taken together they represent convincing evidence that benzene is a human carcinogen.

To date, no clear evidence exists implicating benzene as a carcinogen from animal experiments. A study is in progress at New York University that appears to suggest that inhaled benzene is causing leukemia in rats. At the present time it is felt that it would be premature to base a risk extrapolation on this preliminary data. However, at the completion of this study the CAG will update the present risk analysis to take account of this new information.

III. General Approach to Utilizing Epidemiological Studies to Predict Lifetime Probability of Cancer Deaths Due to Benzene

As was noted in the benzene health document (Goldstein, et al., 1977), very little information exists that can be utilized to obtain a dose response relationship between benzene and leukemia in humans or animals.

However, if a number of simplifying assumptions are made, it is possible to construct crude dose response models whose parameters can be estimated using vital statistics, epidemiological studies, historical workplace benzene standards and monitoring data, and a recent environmental benzene exposure study (Mara and Lee, 1978).

A. Mathematical Model Employed

We assume that for low exposures the lifetime probability of death from leukemia may be represented by the linear equation

$$P = A+Bx$$

where A is the rate in the absence of benzene exposure and x is the average lifetime exposure to atmospheric benzene expressed in ppm. The term B is the change in the leukemia rate for each increase of one ppm of benzene in the air.

If we make the assumption that, "R", the relative risk of leukemia for benzene exposed workers compared to the general population is independent of the length or age of exposure but depends only upon the total exposure, it follows that

$$R = \frac{P_2}{P_1} = \frac{A + B(x_1 + x_2)}{A + Bx_1}$$

or $$RP_1 = A + B(x_1 + x_2)$$

$$P_1 = A + Bx_1$$

so that $$B = P_1(R-1)/x_2$$

where: x_1 = ambient level exposure to benzene

x_2 = industrial level exposure to benzene

P_1 = the lifetime probability of dying of leukemia with no or negligible benzene exposure

To use this model estimates of R and x_2 must be obtained from the epidemiological studies. The exposure values x_1 are derived in the exposure study conducted by SRI dated May 1978 and will be discussed where they are utilized.

The estimate of the lifetime probability of death due to different types of leukemia, P_1, is discussed in detail in the next section.

B. Estimation of Lifetime Probability of Death Due to Various Forms of Leukemia for a Member of the U.S. Population

The data utilized to estimate the lifetime probability of death due to various forms of leukemia is shown in Table 1, which was taken from "Vital Statistics of the United States 1973 Volume II - Mortality Part A." The second and third columns (total deaths and total death rate in 1973) were taken from page 1-184 and 1-8, respectively and utilized to derive column four, total U.S. population in each of the age classes.

The total number of deaths in 1973 due to each of the types of leukemia listed by the 8th ICD code

204 - lymphatic

205 - myeloid

206 - monocytic

207 - other and unspecified

are shown in columns five through eight.

The age specific death rates for each type of leukemia are estimated by dividing the total number of deaths due to that type by the total number of people in that age class.

In the appendix of a 1978 CAG document on population risk due to coke ovens a method referred to as the "constant segmented model" is derived that allows one to estimate the lifetime probability of death due to a disease given the age-specific incidence rates for the disease and all sources of death. This model was employed using the data in Table 1 to obtain the lifetime probabilities of leukemia that approximate as closely as possible the type of leukemia that the relative risk estimates were based upon in each epidemiological study. These lifetime probabilities are shown in Table 2, and will be used subsequently to estimate lifetime probabilities of leukemia death for each unit of exposure to the general population for each of the epidemiological studies.

IV. Epidemiological Studies Utilized

Each of the epidemiological studies is discussed in general. The relative risks are modified in each of the studies to represent a most likely rather than a conservative lower limit as usually is the case where the primary aim of epidemiological workers is to establish with little doubt a "statistically significant" elevated relative risk. Estimates of the average lifetime exposure are also made using as much data as is available. This information is then utilized employing the previously discussed mathematical model to estimate the lifetime probability of leukemia for each unit of exposure.

A. Infante (1977)

1. Description of Infante Study (1977)

In a retrospective study of mortality in a cohort of 748 white male workers in two Ohio plants manufacturing a natural rubber cast film product, Infante et al., (1977) observed a statistically significant higher rate of leukemia than in either of two control groups. The leukemia mortality rate was 5.06 times higher than the general U.S. white male population standardized for age and time period of the cohort exposure, and 4.74 times higher than a cohort of 1447 white males employed at an Ohio fibrous-glass construction products factory. These results were based on a 75% follow-up of the vital status of the workers. A total of 160 deaths were observed and of these there were 7 leukemia deaths, four of which were acute myelogenous, one chronic myelogenous, and two monocytic leukemia.

As with virtually all epidemiological studies, the Infante study has various strengths and shortcomings. Among its strengths are; (1) the worker exposures are said to have been almost exclusively restricted to benzene, since it is used throughout the plant as the principal solvent in all major processes; (2) the individuals in the cohort all worked before 1950 and were followed until 1975, thus allowing long latency diseases to be observed, and (3) acute

myelogenous leukemia was observed, which is the same cell type of leukemia observed in other studies where workers have had known benzene exposures. The disadvantages of relying on this study for determining general population risks are: (1) the authors essentially give no estimate of worker exposures except to say that the levels were less than the prevailing recommended occupational limits at the time various monitoring surveys were made; (2) the members of the cohort study actually worked at two separate plants (Akron and St. Mary's, Ohio). Air monitoring information in the former plant is almost non-existent (Baier, 1977), and therefore the exposure to half of the members of the cohort is almost completely unknown. However, it is known (Young 1977) that the crude rates (leukemia cases/total people in the cohort) are similar in the two locations; (3) Warren et al., (1977) claimed that over 400 workers known to be exposed to low benzene levels were deliberately excluded from the cohort. In spite of these problems, it is felt that this study is the least flawed of the three utilized.

2. Estimation of the Relative Risk

In an update, published as a letter to the editor in Lancet (Benzene and Leukemia, October 14, 1977) Infante et al., note that:

(1) Sakol (1977) has supplied additional information that at least two more cases of leukemia known to exist, but not reported on death certificates, were probably in Infante's cohort;

(2) Due to a more complete follow-up, the expected number of deaths due to leukemia in their cohort was reduced from 1.38 to 1.25.

Using this supplemental information, the new relative risk due to total leukemia is estimated to be

$$R = (7+2)/1.25 = 7.20$$

3. Estimation of Average Occupational Exposure

Information about the plant benzene levels is contained in the Appendix to the testimony of Baier at the OSHA benzene hearings (Baier, 1977). From the opening of the factory in 1940 until 1946, no monitoring records were available. Following the installation of new ventilation equipment in 1946, a survey showed that levels in "most areas" in the plant ranged from 0 to 15 ppm and that all areas had less than the maximum safe limit of 100 ppm which prevailed at that time. From this information, one can guess that the average exposure to all people in the plant before 1946 is probably not much more than 100 ppm, and not less than 15 ppm.

Benzene levels were monitored after 1946 at various plant locations but they were all instantaneous samples and no reliable information is available about how many man-hours were spent at those locations or whether protective masks were worn. These are case reports of exposures to 1000 ppm for short time intervals. Since the average levels were generally close to the occupational standard, we will make the assumption that the average worker exposure was the same as the prevailing recommended occupational limits. These are tabulated below along with the time weighted average for the 36 years of the total exposure period.

Time Interval	No. of Cases	Average Exposure (ppm)	Time-Weighted Average (ppm)
1940-46	(7)	100-15	
1947	(1)	50	39.9-23.3
1948-56	(9)	35	
1957-68	(12)	25	
1969-75	(7)	10	

The actual levels to which the workers were exposed was a subject of heated debate at the OSHA benzene hearings. The CAG would like to see a realistic estimate of the population weighted average exposure and its uncertainty limits. The time-weighted averages for occupational exposure must be converted to a continuous exposure lifetime basis. It will be assumed that the maximum likely lifetime exposure would result if a worker entered the factory in 1940 and was exposed for 35 years to the occupational limit of benzene. This exposure would result in a time-weighted average of 40.36 ppm for 35 years. The least likely exposure is assumed to occur if a worker started in 1950 and was exposed to the occupational limit, which results in a time-weighted average of 23.7 ppm for 25 years. The equivalent continuous lifetime exposures corresponding to these work place exposure estimates are:

$$\text{High estimate: } 40.36 \times \frac{240}{365} \times \frac{1}{3} \times \frac{35}{70} = 4.4\text{ppm}$$

$$\text{Low estimate: } 23.7 \times \frac{240}{365} \times \frac{1}{3} \times \frac{25}{70} = 1.8\text{ppm}$$

The geometric mean of the high-low exposures, $\sqrt{4.4 \times 1.8} = 2.81$, is taken to be the best estimate of the lifetime average for workers in the cohort.

4. Estimation of Lifetime Probability of Leukemia Per Unit of Exposure

The change in the leukemia rate per lifetime average ppm in the atmosphere is derived from the previously discussed equation:

$$B = P_1 (R-1)/x_2$$

which gives us an estimate

$$B = .006732 \times (7.20-1)/2.81 = .014854$$

B. Askoy (1974, 1976, 1977)

1. Description of Askoy Studies

Askoy (1977, 1976, 1974) has reported his observations of the occurrence of leukemia and aplastic anemia cases at two medical institutions in Istanbul over a period from 1967 to 1975. He has compared the types of leukemia seen in shoe workers, who work with benzene solvents in small unventilated shops, with the types of leukemia observed in people with no known exposure to benzene. He has also tabulated the exposure duration of patients with different types of leukemia. He found that in shoe workers there were 34 cases of leukemia observed in the nine years from 1967 to 1975. Based on "official records" which show that in Istanbul there are 28,500 workers in the shoe, slipper and handbag industry, he calculates that the annual incidence

rate of leukemia is 13 per 100,000, which is significantly higher than 6 per 100,000, the rate in the general population. The calculation is based on crude rates with no age adjustment.

He also found that the types of leukemias occurring in people exposed to benzene are different than for those with no known exposure. In a sample of 50 non-exposed leukemia patients, approximately 50 percent had chronic leukemia, but in 40 benzene-exposed patients only 5 percent had chronic leukemia. Also, in the exposed group preleukemia and acute erythroleukemia accounted for 34 percent of the cases, whereas in the non-exposed group only 6% of the cases were of those types.

The concentration of benzene to which the workers were exposed was estimated only in terms of the maximum concentrations existing at the times when benzene was being used in the shops. At the OSHA benzene hearings in 1977 Dr. Askoy stated that the concentrations outside working hours ranged between 15 and 30 ppm and reached a maximum of between 150 and 210 ppm when adhesives containing benzene were being used.

2. Estimation of Relative Risk

A total of 26 patients with leukemia were observed in the 6 2/3 year period from 1966 to September 1973 in a group of 28,500 Instanbul shoe workers exposed chronically to benzene. This was felt to be an underestimate of the true number of leukemia cases among the shoe workers during the period with Askoy subsequently being aware of two additional cases. However, three of the twenty-eight total cases were lymphoblastic or lymphoid leukemia, not thought to be associated with benzene exposure. Eliminating these three cases, an estimate of the yearly incidence rate is

$$I = \frac{(26+2-3) \times 10^5}{28{,}500 \times 6.67} = 13.15 \text{ per } 100{,}000 \text{ per year}$$

The total incidence rate of leukemia in Turkey is thought to be about 2.5 to 3.0 per 100,000 Askoy (1977). However from Askoy's non-exposed patient group we estimate that 48% based on 24 out of 50 are non-lymphoblastic or lymphoid leukemia. In addition, the national rate which is based on the total population was felt by Cooke (1954) to be about twice that experienced for the relatively young group of benzene-exposed shoe workers who had a average age at diagnosis of 34.2 years. Using this information we estimate that the yearly incidence rate of non-lymphoblastic or lymphoid leukemia in the Turkish population of the same age structure as the benzene exposed shoe workers is

$$I = \frac{(2.5+3.0)}{2} \times \frac{24}{50} \times \frac{1}{2} = .66 \text{ per } 100{,}000$$

An estimate of the relative risk for benzene exposed shoe workers is thus

$$R = \frac{13.15}{.66} = 19.92$$

3. Estimation of Lifetime Average Exposure

It was noted that the benzene levels were 15 to 30 ppm outside working hours and 150 to 210 ppm during working hours when benzene was in use in the typical small shoe manufacturing shop. We will assume that the average working hour exposure to benzene was the geometric mean of the midpoint of the two intervals or

$$x_2 = \sqrt{\frac{(15 + 30)}{2} \times \frac{(150 + 210)}{2}} = 63.6 \text{ ppm}$$

In addition we will assume:

(1) A ten hour working day

(2) A 300 day working year

(3) An average age at the end of the observation period of 50 years

(4) An average of 9.7 years of exposure; this is the average length of exposure for the leukemia cases in Askoy's series.

These assumptions lead to a lifetime average exposure estimate of

$$x_2 = 63.6 \times \frac{10}{24} \times \frac{300}{365} \times \frac{9.7}{50} = 4.22 \text{ ppm}$$

4. Estimation of Lifetime Probability of Leukemia Per Unit of Exposure

The change in the leukemia rate per lifetime average ppm in the atmosphere is derived from the previously discussed equation:

$$B = P_1(R-1)/x_2$$

which gives us an estimate

$$B = .004517 \times (19.92-1)/4.22 = .020252$$

C. Ott, et al., (1977)

1. Description of Ott Study

The long-term mortality patterns and associated exposure estimation of a cohort of 594 workers exposed to benzene were reported by Ott, et al., (1977). The workers were employed in three production areas of the company, which had been in operation for varying times since 1920.

Each job category was assigned an average exposure range as accurately as the historical air monitoring data permitted. The concentrations ranged from less than 2 ppm (8-hour time weighted average) to greater than 25 ppm. The analysis covered employees with known benzene exposure who

worked from January 1, 1940 through 1973. A total of 53 employees with known exposure to arsenicals, vinyl chloride and asbestos in addition to their benzene exposure was omitted from the formal cohort of people exposed to benzene.

The benzene exposure of each person was evaluated and ex-pressed as the product of parts per million times months of exposure. For the 91 deceased people with exposure to benzene alone, 45% of them had exposures between 0 and 499 ppm-months and 35% had exposures greater than 1000 ppm-months. The results of the analysis of mortality by cause of death showed no statistically significant excess of mortality compared to the U.S. white male age-specific mortality rates. Three cases of leukemia were observed where 0.8 cases were expected, a situation of borderline statistical significance ($p<0.047$). All three were myelocytic leukemia, two of them acute, which latter is the type associated with benzene exposure of shoe workers (Askoy, 1976) and other occupations (Vigliani, 1976).

2. Estimation of Relative Risk

In Ott's cohort 3 deaths due to non-lymphocytic non-monocytic leukemia were observed with only .8 expected. An estimation of the relative risk of non-lymphocytic - monocytic leukemia is thus

$$R = 3/.8 = 3.75$$

3. Estimation of Lifetime Average Exposure

Ott estimated the ppm-months of exposure of each individual in his cohort from work history data and plant hygiene benzene measurement surveys. The most complete presentation of this data is given in Ott's (1977) table 7 which is used to estimate the average level of exposure.

It is assumed that the average exposure in each of the exposure intervals is equal to the midpoint of the first two intervals and is equal to the lower limit plus 1/2 of the interval width for the open or third classification. The total average ppm-months is obtained by taking the average of the three classifications weighted by the expected value of the number of deaths in each classification giving the value

$(250 \times 65.1 + 750 \times 16.2 + 1250 \times 32.8)/(65.1 + 16.2 + 32.8)$
$= 608.46$ ppm x months

The average lifetime exposure is obtained by using the following assumptions:

(1) An eight hour working day

(2) A 240 day working year

(3) An average age at the end of the observation period of 65 years

which gives the lifetime estimate of

$$\left(\frac{608.46}{12}\right) \times \left(\frac{8}{24}\right) \times \left(\frac{240}{365}\right) \times \left(\frac{1}{65}\right) = .171 \text{ ppm}$$

4. Estimation of Lifetime Probability of Leukemia Per Unit of Exposure

The change in the leukemia rate per lifetime average ppm in the atmosphere is derived from the previously discussed equation:

$$B = P_1(R-1)/x_2$$

which gives us an estimate

$$B = .002884 \times (3.75-1.)/.17 = .04638$$

D. Summary of Results

The total leukemic response has been based on different classifications of leukemia for the three studies. A summary of the type of response utilized is given in Table 3. It would have been preferable to have applied a uniform method of classification for all the studies. However, due to the lack of specific detail in the presented papers this was not possible.

Even with this added source of variability the resulting slope estimates B, which have the physical meaning of the total probability of deaths due to 1 ppm of benzene in the air breathed over an individual lifetime, were remarkably consistent between studies. The geometric mean of the three estimates is

$$B = \sqrt[3]{.014854 \times .020252 \times .046380} = .024074$$

The estimated log mean is

$\log_{10}B = -1.618453$, with the estimated variance of this mean being $\sigma^2_{\log B} = .021785$

V. Estimation of Expected Number of Leukemia Deaths Due to Environmental Exposure to Benzene

The SRI in their exposure document expressed exposure to the U.S. population in two ways.

The first method assumed a static population living around the point sources and gave total ppb-person years for each of the point source classifications in Table I-1.

If exposure units in 10^6 ppb-person years are denoted as D, the expected number of leukemia deaths per year may be estimated approximately by the relationship

$$N_D = .024074 \times D \times 10^3/70.96 = .339262D$$

where .024074 is the geometric mean of the slope parameter taken from the three studies, and 70.96 is the average expected life of a randomly drawn person living in the United States based on 1973 vital statistics.

Using Table I-1 and the above equation the number of leukemia deaths per year are estimated for the various point sources and are shown in Table 4.

The second method employed to estimate exposure did not make the over-simplified assumption that the human population was static. Instead an attempt was made to follow a typical individual through a typical day in order to obtain his average exposure. The exposure estimates derived on this basis are shown in Table I-2 of the SRI document and were utilized in conjunction with the above equation to derive the estimated number of leukemia deaths per year shown in Table 5.

We note that approximately a total of 90 cases of leukemia per year could be expected due to benzene exposure. In a recent CAG document on POM's, a method was developed to obtain confidence intervals for estimates based upon the assumptions that each epidemiological study gave an unbiased estimate of the true slope parameter and the estimates were distributed log normally. Adding the additional assumption that the exposure estimates are also log normally distributed we derive the relationship that the 95% confidence interval for the log of the number of leukemia deaths per year is

$$1.953289 \pm \sqrt{.083689 + \log^2 u}$$

where we are 95% confident that the true exposure is between $(u-1) \times 100\%$ and $(u-1)^{-1} \times 100\%$ of the exposure estimate.

The confidence limits derived from this relationship for various assumed values of u are shown in Table 6.

TABLE 1 - Data Utilized to Estimate Lifetime Probability of Death Due to Various Forms of Leukemia

Age Interval	Total Deaths TD	Total Death Rate x 10^5 TDR	Total People TP=TD/TDR x10^5	Total Number of Deaths Due to ICD CODE NUMBERS 204	205	206	207
0-1	55,581	1,805.2	30.7894	17	7	3	13
1-5	10,843	79.5	136.3899	157	74	4	93
5-9	7,514	41.5	181.0602	368	64	4	125
10-14	8,468	40.6	208.5714	211	88	6	92
15-19	22,908	111.9	204.7185	174	175	8	98
20-24	26,549	146.8	180.8515	76	141	4	65
25-29	22,205	143.5	154.7387	43	194	13	50
30-34	21,512	165.7	129.8250	28	181	9	54
35-39	26,374	235.1	112.1821	28	211	11	55
40-44	40,913	355.2	115.1830	36	241	19	68
45-49	67,349	563.3	119.5615	76	327	24	96
50-54	98,667	832.8	118.4762	131	407	28	134
55-59	133,604	1,314.5	101.6387	250	502	29	196
60-64	176,973	1,943.9	91.0402	370	576	42	262
65-69	213,495	2,804.7	76.1204	477	722	49	317
70-74	241,166	4,302.7	56.0499	515	794	70	376
75-79	263,251	6,722.4	39.1603	651	730	79	357
80-84	250,985	9,777.4	25.6699	576	522	39	311
85+	284,400	17,429.4	16.3173	469	364	47	254
TOTAL			209.8344 x 10^6				

TABLE 2 - Lifetime Probability of Death in U.S. Population Due to Leukemia Type Upon Which Relative Risk in Each of the Epidemiological Studies is Based

Epidemiological Study	ICD Codes Utilized	Type of Leukemia	Lifetime Probability of Death Due to Type of Leukemia
Infante	204-207	Total Leukemia	.006732
Ott	205	Myelogenous	.002884
Askoy	205-207	Non-Lymphatic	.004517

TABLE 3 - Summary of Data Used to Estimate Lifetime Probability of a Leukemia Death Per ppm Benzene Lifetime Exposure

Study	R Relative Risk Estimate	x_2 Estimate Average Lifetime Exposure	P_1 Lifetime Probability of Leukemia	B Estimated Slope Parameter
Infante	7.20	2.81	.006732	.014854
Askoy	19.92	4.22	.004517	.020252
Ott	3.75	.17	.002884	.046380

TABLE 4 - Source Specific Benzene Caused Leukemia Deaths/Year Based on Table I-1 of SRI Benzene Exposure Document[a]

Source of Exposure	10^6 x ppb-Person Years Exposure in	Expected Number of Benzene Caused Leukemia Deaths/Year
Chemical Manufacturing	8.5	2.88
Coke Ovens	.2	.07
Petroleum Refineries	2.5	.85
Automobile Emissions	150.0	50.89
Gasoline Service Stations	19.0	6.44
Self Service Gasoline	1.6	.54
TOTAL	181.8	61.67

[a]Mara, Susan J. and Shonh S. Lee. Assessment of Human Exposures to Atmospheric Benzene. SRI International for U.S. Environmental Protection Agency, Research Triangle Park, NC. Publication No. EPA-450/3-78-031. June 1978.

TABLE 5 - Total Exposure of People Residing in Various Locations, and Resulting Estimated Benzene-Caused Leukemia Deaths/Year - Based on Table I-2 of SRI Benzene Exposure Document[a]

Vicinity of Residence	Exposure in 10^6 ppb-Person Years	Expected Number of Benzene-Caused Leukemia Deaths/Year
Chemical Manufacturing	10.0	3.39
Coke Ovens	.2	.07
Petroleum Refineries	4.5	1.53
Urban Areas	250.0	84.80
TOTAL	264.7	89.80

[a]Mara, Susan J. and Shonh S. Lee. Assessment of Human Exposures to Atmospheric Benzene. SRI International for U.S. Environmental Protection Agency, Research Triangle Park, NC. Publication No. EPA-450/3-78-031.

TABLE 6 - Confidence Limits on Total Benzene Caused Leukemia Deaths Per Year (Assumes "One-Hit" Model is the True Dose Response Relationship)

Level of Precision Assumed for Exposure Estimate (U-1) x 100%	95% Confidence Limits Lower Limit	Upper Limit
0%*	46.1	174.8
10%	45.8	176.0
50%	41.2	195.9
100%	34.3	234.9
1000%	7.5	1081.7

*Assumes no error in exposure estimate.

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VII. APPENDIX

Mutagenic Risks of Benzene Exposure

Summary

In addition to the risk from leukemia, benzene exposure is also likely to induce inherited mutations. The magnitude of this risk can not be estimated because of the uncertain quantitative relationship between heritable mutations and chromosome aberrations which have been consistently observed in exposed workers.

Review of Experimental Results

Benzene was found to be non-mutagenic in the Ames' test for point mutational effects (Simmon et al., 1977; Shahin, 1977; and Lyon, 1975). However, it is possible that a human metabolic activation enzyme system or a mammalian body fluid activation system would cause it to be mutagenic.

Somatic chromosomal aberrations have been demonstrated in animals and humans. In rabbits, Kissling and Speck, 1971 reported the induction of cytogenetic damage *in vivo* by subcutaneous injection of 0.2 ng/kg day benzene. The frequency of metaphase spreads showing aberrations (mostly gaps and breaks) increased from 5.9% to 57.8% after an average exposure interval of 18 weeks. Two months after discontinuance of the benzene treatment, cytogenetic damage was still observed.

Dobrokhotov (1972) exposed rats to 0.2 g/kg day benzene and 0.8 g/kg day toluene, and found similar rates of chromosomal aberrations in the two chemicals given separately, and an additive effect when given together. Chromatic deletions in metaphase chromosomes of bone-marrow cells have been found in rats given single doses of benzene subcutaneously at 2 ml/kg (Philip and Jensen, 1970). Deletions have also been observed in rats given benzene at 1g/kg day, subcutaneously, for 12 days.

A dominant lethal and in vivo cytogenetics combined test has been performed with rats dosed intraperitoneally with 0.5 ml/kg benzene (Lyon; 1975). No dominant lethality was found but increases were found in chromatic and chromosomal aberrations. Lyon (1975) also found increased micronuclei counts 6 hours after the final dosing of rats at 0.05 and 0.25 ml/kg/day after two days of dosing intraperitoneally.

In patients with benzene-induced aplastic anemia, lymphocyte chromosome damage has been found (Pollini and Colombi, 1964). Polini et al., (1964) later found a 70% incidence of heteroploid chromosomal patterns in the blood lymphocytes and bone marrow parenchyma cells of each of four subjects with benzene-induced blood dyscrasias. Similar patient studies of benzene exposed individuals with

persistent chromosomal alterations associated with blood dyscrasias have also been reported by others (Forni and Moreo, 1967, 1969; Hartwich et al., 1969; Khan and Khan, 1973; Sellzei and Kelemen, 1971; Forni et al., (1971); Tough and Court Brown, 1965).

Vigiliani and Forni (1969) found a significant increase of chromosomal aberrations in pheripheral lymphocytes of workers exposed to benzene, but not in those exposed to xylene and toluene. Some of these aberrations persisted for several years after recovery from benzene hemopathy. They suggested that toxicity to the bone marrow might result in cells with an abnormal number of chromosomes and that proliferation of these cells could then give rise to an advantaged leukemic clone. Forni et al., (1971) examined chromosomal aberrations in 34 workers in a rotogravure plant and compared these to 24 matched controls, and found a significantly higher number of both stable and unstable aberrations in 10 benzene-exposed workers but a number comparable to controls in all of the 24 toluene-exposed workers.

A recent report (Kilian and Daniels, 1978) on 52 workers exposed to benzene for one month to 26 years (mean of 56.6 months) found chromosomal aberrations (chromosome breaks, dicentric chromosomes, translocations and exchange figures)

in peripheral lymphocytes at 2-3 times the rates found in controls. In this study, the 8 hour average time-weighted benzene exposure was 2-3 ppm, the average concentration determined by 15 minute sampling was 25 ppm and the peak concentration was 50 ppm.

The same laboratory reported on the monitoring of 471 peripheral lymphocyte cultures from 290 Texas Division benzene workers between 1965 and 1978 (Benge et al., 1978). A group of 972 "preemployment examinees" who were judged, on the basis of the history taken at the time, to have had negligible exposure to known chromosome-breaking agents were used as controls. Rates of chromosomal abnormalities were found not to be increased in the exposed group over the control group. The time-weighted average benzene concentrations were estimated to have been below 50 ppm prior to 1972 and well below 10 ppm from 1973 to the present time.

A report by Picciano (1978) which is a further analysis of the Kilian and Daniel (1978) and Benge (1978) study comparing the information on benzene exposed individuals to a 44-person group seen for preemployment examination. Workers exposed to three different levels of benzene at less than 10 ppm for several years showed a dose response relationship. The types of aberrations detected are similar to those reported for higher benzene exposures by (Tough et

al., 1970). The workers were monitored for urinary excretion of phenol which is a primary metabolite of benzene. All workers had no detectable phenol which indicated no recent exposure to benzene. Exposures for the dose-response relationship were 0, less than 1, 1-2.5 and greater than 2.5 ppm.

Fredga et al., (1978) performed a study on 65 workers, occupationally handling motor fuels. A moderate, but statistically significant, increase in frequency of chromosome aberrations was found in road tanker drivers and industrial workers, but not in ship tanker crews and gasoline station staff. The estimated exposure dose was 60 ppm or less. The dose absorbed will be reported in a subsequent study.

Conclusions

Ample evidence exists that benzene causes chromosomal aberrations in animals and humans exposed to benzene. This evidence was reviewed above. However, since this is a somatic cell effect as opposed to a germinal cell effect it is difficult to estimate the heritable risk to future generations from such evidence. These chromosomal aberrations probably involve breaks in DNA and therefore are heritable events if they occur in the germinal cells, although the experiments to prove that point have not been decisive.

It is generally recognized that rings, dicentrics, translocations and exchange figures are heritable, but chromosome breaks could be caused from toxicity of somatic cells and therefore may not be heritable. The former lesions should be used as indicators that genetic damage to future generations may have occurred. At the current time quantitative estimates of heritable genetic damage due to benzene cannot be made from data on the frequency of somatic mutations, although this damage may be occurring at concentrations as low as 1 ppm in air.

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